The evidence-based nutritional support of the oncologic patient

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TOPICS

• Rationale for the nutritional support
  the evidence from RCT
  the clinical/biologic plausibility
• Evidence for oral/enteral nutrition
• Evidence for parenteral nutrition
• The clinical approach
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# Grades of recommendations and levels of evidence

<table>
<thead>
<tr>
<th>Grades of recommendation</th>
<th>Levels of evidence</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ia</td>
<td>Meta-analysis of randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Ib</td>
<td>At least one randomized controlled trial</td>
</tr>
<tr>
<td>B</td>
<td>IIa</td>
<td>At least one well-designed controlled trial without randomization</td>
</tr>
<tr>
<td></td>
<td>IIb</td>
<td>At least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case-control studies</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>Expert opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>
Recommendations for the NS of nonsurgical cancer patients in international guidelines

<table>
<thead>
<tr>
<th>Grade %</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPEN (2002) (N°12)</td>
<td>33</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>ESPEN (2006) enteral (N°25)</td>
<td>12</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>ESPEN (2009) parent (N°18)</td>
<td>11</td>
<td>17</td>
<td>72</td>
</tr>
</tbody>
</table>
SPECIAL ARTICLE

EQUIPOISE AND THE ETHICS OF CLINICAL RESEARCH

Benjamin Freedman, Ph.D.

Abstract  The ethics of clinical research requires equipoise — a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment. The current understanding of this requirement, which entails that the investigator have no “treatment preference” throughout the course of the trial, presents nearly insuperable obstacles to the ethical commencement or completion of a controlled trial and may also contribute to the termination of trials because of the failure to enroll enough patients.

I suggest an alternative concept of equipoise, which would be based on present or imminent controversy in the clinical community over the preferred treatment. According to this concept of “clinical equipoise,” the requirement is satisfied if there is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the preferred treatment. (N Engl J Med 1987; 317: 141-5.)

“...the ethics of clinical research requires a state of genuine uncertainty on the part of the clinical investigator or the expert medical community regarding the comparative therapeutic merits of each arm in a trial...”
Survival of healthy subjects under total macronutrient deprivation

63 days  (BW loss 41%)°
57-73 days  (BW loss 40%)°°

° American taylor starver
°° Irish hunger strikers
**PN in the incurable cancer patient: therapy, support or something in between?**

**PN is a therapy**

- *Drug is any chemical agent which affects living processes (Goodman&Gilman 1941)*
- Physicians prescribe PN
- Physicians and medical societies consider nutrition as a therapy
- PN is a medical therapy for ill people
- It should be validated by RCT

**PN is a support**

- Also “natural” nutrition affects living processes (Paradoxically all humans got intrauterine PN)
- Dietitians prescribe PN in USA and patients and relatives often ask for it
- Nourishment is viewed by the relatives as an act of love and care
- Nutrition is essential both to ill and healthy people
- It is ethically impossible to have a no-PN arm and hence a GRADE A recommendation
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Malnutrition is an independent negative prognostic factor

- Weight loss

- Low bioelectric phase angle

- Depletion of body protein or fat
  - van Vledder et al 2012
  - Murphy et al 2010

- Prognostic Nutritional Index
  - Nozoe et al., 2002, 2010

- Glasgow prognostic score
  - Crumley et al 2006
Malnutrition adversely affects quality of life

• higher rates of hospital readmissions, longer hospital stay (Correja et al. 2003, Pressoir et al., 2010),
• increased symptom distress (Sarna et al., 1994)
• reduced muscle strength and functional status (Norman et al. 2010)
Malnutrition increases chemotherapy toxicity

- Weight loss and hypoalbuminemia (Arrieta et al. 2010).
- Low total body nitrogen is a predictor of neutropenia (Aslani et al., 2000).
- Sarcopenia is a significant predictor of toxicity and time-to-progression (Prado et al., 2009).
- BMI < 25 kg/m² is a significant predictor of toxicity (Antoun et al., 2010).
Malnutrition impairs the response to chemotherapy

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AIMS: to test whether AA can acutely stimulate muscle protein synthesis in cancer patients (CA) undergoing intense chemotherapy.

METHODS: ingestion of 40 g of AA given in 30 mL boluses every 10 min for 3h.

Mixed muscle fractional synthetic rate (FSR) in the basal state (white bars) and in response to amino acids (black bars). **Significantly different than basal, P≤0.001. From Dillon 2007

OBJECTIVE: to determine if a specially formulated medical food, high in leucine and protein, stimulates muscle protein synthesis acutely in individuals with cancer to a greater extent than a conventional medical food.

DESIGN: The experimental group (n = 13) received a medical food containing 40 g protein, based on casein and whey protein and enriched with 10% free leucine and other specific components, while the control group (n = 12) was given a conventionally used medical food based on casein protein alone (24 g).

RESULTS: medical food increased significantly muscle protein FSR. In contrast, ingestion of the control medical food did not increase muscle FSR.
RCT on oral nutritional supplements during RT

Five RCT (Arnold et al., 1989, Bounous et al., 1975, Moloney et al., 1983, Nayel et al., 1992, Douglass et al., 1978) showed a nutritional benefit in cancer patients (mainly head-neck) undergoing RT.
RCT on oral nutritional supplements and counseling during RT

- reduction of the adverse effects of RT and better quality of life functions scores (*Ravasco et al.* 2005)
RCT on oral nutritional supplements during CT

No evidence of benefit in a RCT (Tandon et al., 1984) and 3 non-RCT (Elkort et al., 1981, Evans et al., 1987) in non malnourished patients except a better preservation of the albumin serum (DeVries et al., 1982).
n-3 enriched oral nutritional supplements

The more recent ASPEN Guidelines (August et al., 2009) state that n-3FA supplementation may help to stabilize weight in cancer patients on oral diets experiencing progressive unintentional weight loss (TYPE 2 evidence)
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PN as an adjunct to chemotherapy
EVIDENCE from LITERATURE

AMERICAN GASTROENTEROLOGICAL ASSOCIATION MEDICAL POSITION STATEMENT: PARENTERAL NUTRITION
(Gastroenterology 121:966-969; 2001)

AGA TECHNICAL REVIEW ON PARENTERAL NUTRITION
(Gastroenterology 121:970-1001; 2001)
**Table 5. Meta-Analysis of Oncologic Trials**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Absolute risk difference&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Confidence intervals</th>
<th>Number of studies (patients) included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0%</td>
<td>−5%, +5%</td>
<td>19 (1050)</td>
</tr>
<tr>
<td>Total complication rate</td>
<td>+40%</td>
<td>+14%, +66%</td>
<td>8 (333)</td>
</tr>
<tr>
<td>Infectious complication rate</td>
<td>+16%</td>
<td>+8%, +23%</td>
<td>18 (823)</td>
</tr>
<tr>
<td>Tumor response</td>
<td>−7%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−12%, −1%</td>
<td>15&lt;sup&gt;d&lt;/sup&gt; (910)</td>
</tr>
<tr>
<td>Bone marrow toxicity</td>
<td>+22%</td>
<td>−10%, +54%</td>
<td>3 (134)</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>+1%</td>
<td>−9%, +11%</td>
<td>6 (310)</td>
</tr>
</tbody>
</table>

<sup>a</sup>This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.

<sup>b</sup>Although 1 bone marrow transplantation trial reported an improved survival,<sup>94</sup> this was not demonstrated when all 4 trials<sup>91-95</sup> were combined; absolute risk difference equaled −5% (−14%, +5%). Only 3 of these trials provided parenteral nutrition during the time when the transplantation was performed<sup>92-95</sup>; when only these 3 trials were combined, absolute risk difference equaled −9% (−22%, +4%).

<sup>c</sup>A negative absolute risk difference indicates that the response rate in the control group was higher than in the recipients of the parenteral nutrition.

<sup>d</sup>13 of these 15 RCTs were chemotherapy trials.
Effects of TPN on pts receiving oncologic therapy

19 RCTs (1050 pts)

- No benefit on mortality
- Increase in total complications rate
- No constant effect on tumor response
- No protection against bone marrow or GI toxicity
Major criticism

• >90% of these RCTs published before 1990
• Nutritional regimens suboptimal as regards composition and duration
• Severe malnutrition was not a criteria for entering pts in the RCTs
Improved Clinical Outcomes in Patients With Advanced Esophageal Cancers Utilizing Supplemental Parenteral Nutrition

- Patients receiving PN support were able to tolerate higher doses of chemoradiation therapy without increased toxicity.

PN in chemotherapy patients

According to the last ASPEN and ESPEN GL

• the routine use of PN during chemotherapy is not recommended. (Grade B).
• If patients are malnourished or facing more than a week of starvation and an enteral nutritional support is not feasible, PN is recommended (Grade B).
• If patients develop gastrointestinal toxicity from CT or RT, short-term PN is usually better tolerated (and efficient) than EN to restore the intestinal function and preventing a nutritional deterioration (General consensus).
SUPPLEMENTAL (H)PN

... is a partial PN and is not used in aphagic-obstructed-incurable cancer patients, but in an earlier phase of the disease when oral food intake starts declining and patients who may or may not be receiving some kind of oncologic therapy, continuously lose their body weight...
SUPPLEMENTAL HPN
(5 RCTs)


Problems with the German study

● Design of the study
weight-losing advanced cancer pts received for several wks 30 Kcal+1.54 g AA/Kg by oral or iv route

● Results
PN associated with benefit in BMI, BCM, QoL, toxicity and survival

But...
- it is quite uncommon for advanced GI cancer pts to maintain till death a volitional oral intake of 30 kcal/Kg/d
309 patients with progressive cachexia and receiving indomethacin, EPO and iron (when necessary) were randomized to HPN or no HPN when oral intake dropped to 21-24 Kcal/Kg

At intention-to-treat basis:  \( \uparrow \) energy balance
As-treated analysis: \( \uparrow \) energy balance
\( \uparrow \) survival
\( \uparrow \) maximum exercise capacity

Total AA intake g/Kg/d: \( \sim 0.8 \) (ent) + 0.6-0.9 (iv)
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The clinical approach

• screen the nutritional status (SGA, MUST, NRS 2002)

• Plan the appropriate nutritional support
### Nutritional Risk Screening (NRS 2002)

#### Table 1 Initial screening

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is BMI &lt;20.5?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Has the patient lost weight within the last 3 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Has the patient had a reduced dietary intake in the last week?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Is the patient severely ill? (e.g. in intensive therapy)</td>
<td></td>
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</tbody>
</table>

**Yes:** If the answer is 'Yes' to any question, the screening in Table 2 is performed.  
**No:** If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

#### Table 2 Final screening

<table>
<thead>
<tr>
<th>Absent: Score 0</th>
<th>Impaired nutritional status</th>
<th>Severity of disease (± increase in requirements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal nutritional status</td>
<td>Mild Score 1: Wt loss &gt;5% in 3 mths or Food intake below 50-75% of normal requirement in preceding week</td>
<td>Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*, Chronic hemodialysis, diabetes, oncology</td>
</tr>
<tr>
<td>Mild Score 1</td>
<td>Highly impaired general condition or Food intake 25-60% of normal requirement in preceding week</td>
<td>Mild Score 1</td>
</tr>
<tr>
<td>Moderate Score 2</td>
<td>Severe Score 3: Wt loss &gt;5% in 1 mth (&gt;15% in 3 mths) or BMI &lt;18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week</td>
<td>Major abdominal surgery* Stroke* Severe pneumonia, hematologic malignancy</td>
</tr>
<tr>
<td>Severe Score 3</td>
<td>Severe Score 3: Wt loss &gt;5% in 1 mth (&gt;15% in 3 mths) or BMI &lt;18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week</td>
<td>Head injury* Bone marrow transplantation* Intensive care patients (APACHE&gt;10).</td>
</tr>
</tbody>
</table>

Score: + Score: = Total score
NRS 2002
(Bozzetti et al. Support Care Cancer. 2012 Feb 7)

• 1453 cancer outpatients were screened
• 32% identified at nutritional risk
• Nutritional risk associated with primary tumour site
  ECOG
  Presence of anorexia or fatigue
The clinical approach

- screen the nutritional status (SGA, MUST, NRS 2002)
- plan the appropriate nutritional support
The clinical approach to nonsurgical cancer patients at nutritional risk

1. Patients with all GI tract working:
   - try first with oral supplements (better if ω3 and/or leucine enriched) +/- counseling and megestrol
   - consider supplemental PN

2. If upper GI tract is not accessible:
   consider tube feeding (NG, NJ, PEG)

3. If all GI tract is not accessible/working:
   consider TPN
...knowledge is the enemy of disease...
Survival of patients with inoperable malignant obstruction treated at home

19 days (Mercadante 1995)
21 days (Portio 2011)